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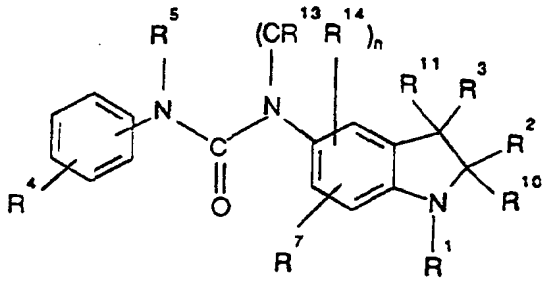
(54) **Title:** 5HT2B RECEPTOR ANTAGONISTS CONDENSED INDOLES

(57) **Abstract**

Compounds of formula (I) wherein: R^2, R^3, R^{10} and R^{11} are independently hydrogen or alkyl, or R^{10} and R^{11} together form a bond, or R^2 and R^{10} or R^3 and R^{11} together form a C^{2-6} alkylene chain, and n ≠ 5 2 or 3. Compounds of formula (I) have $5HTC_{2C}$ receptor antagonist activity, and certain compounds are potential $5HT_{2B}$ antagonists. Compounds of the invention are believed to be of potential use in the treatment of CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, Alzheimer's disease, sleep disorders, feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of certain GI disorders such as IBS as well as microvascular diseases such as macular oedema retinopathy.



(I)

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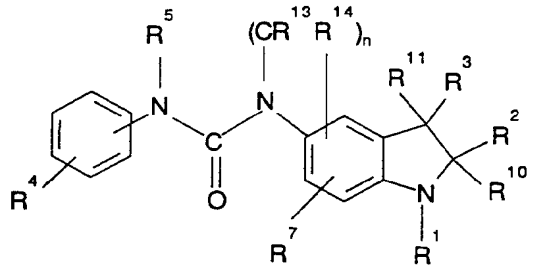
5HT2B receptor antagonists condensed indoles

This invention relates to compounds having pharmacological activity, to a process for their preparation, to compositions containing them and to their use in the treatment of mammals.

WO 92/05170 describes certain urea derivatives which are described as possessing $5HT_{1C}$ receptor antagonist activity. The $5HT_{1C}$ receptor has recently been reclassified as the $5HT_{2C}$ receptor [P. Hartig **et al.**, Trends in Pharmacological Sciences (TIPS) 1993].

A structurally distinct class of compounds has now been discovered, which compounds have been found to have $5HT_{2C}$ receptor antagonist activity. Some or all of the compounds of the invention are also potential $5HT_{2B}$ receptor antagonists, the $5HT_{2B}$ receptor being previously known as the fundus receptor [P.Hartig **et al.**, Trends in Pharmacological Sciences (TIPS) 1993]. $5HT_{2C}$ /$5HT_{2B}$ receptor antagonists are believed to be of potential use in the treatment of CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, Alzheimers disease, sleep disorders, feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of certain GI disorders such as IBS as well as microvascular diseases such as macular oedema and retinopathy.

Accordingly, in a first aspect, the present invention provides a compound of formula (I) or a salt thereof:



(I)

wherein:

R^1 is hydrogen or C_{1-6} alkyl;

R^2, R^3, R^{10} and R^{11} are independently hydrogen or C_{1-6} alkyl, or R^{10} and R^{11} together form a bond, or R^2 and R^{10} or R^3 and R^{11} together form a C_{2-6} alkylene chain;

R^4 is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, halogen, nitro, trifluoromethyl, cyano, CO_2R^{12} or $CONR^{15}R^{16}$ wh(·e R^{12}, R^{15} and R^{16} are independently hydrogen or

C_{1-6} alkyl, $S(O)_nR^{17}$ or $S(O)_nNR^{18}R^{19}$ where n is 1 or 2 and R^{17}, R^{18} and R^{19} are independently hydrogen or C_{1-6} alkyl;

R^5 is hydrogen or C_{1-6} alkyl;

R^7 is hydrogen, C_{1-6} alkyl, OR^{12} or halogen, where R^{12} is hydrogen or C_{1-6} alkyl; and

n is 2 or 3; and

the groups R^{13} and R^{14} are independently hydrogen or C_{1-6} alkyl.

C_{1-6} alkyl moieties can be straight chain or branched and are preferably C_{1-3} alkyl, such as methyl, ethyl, n- and iso- propyl.

Suitably R^1 is hydrogen or C_{1-6} alkyl such as methyl, ethyl or propyl. Preferably R^1 is C_{1-6}alkyl such as methyl.

Suitably R^2, R^3, R^{10} and R^{11} are independently hydrogen or C_{1-6} alkyl, or R^{10} and R^{11} together form a bond, or R^2 and R^{10} or R^3 and R^{11} together form a C_{2-6} alkylene chain. Preferably R^2 is hydrogen. Preferably R^3 is hydrogen.

In an indoline structure, R^{10} and R^{11} are preferably hydrogen.

Suitably R^4 is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, halogen, nitro, trifluoromethyl, cyano, CO_2R^{12} or $CONR^{15}R^{16}$ where R^{12}, R^{15} and R^{16} are independently hydrogen or C_{1-6} alkyl, $S(O)_nR^{17}$ or $S(O)_nNR^{18}R^{19}$ where n is 1 or 2 and R^{17}, R^{18} and R^{19} are independently hydrogen or C_{1-6} alkyl. Preferably R^4 is nitro, cyano, halo, carbamoyl, C_{1-6}alkoxy or trifluoromethyl.

Suitably R^5 is hydrogen or C_{1-6} alkyl. Preferably R^5 is hydrogen.

Suitably R^7 is hydrogen, C_{1-6} alkyl, OR^{12} or halogen, where R^{12} is hydrogen or C_{1-6} alkyl. The group R^7 can be attached to any vacant position in the phenyl part of the indole or indoline rings, that is to say, the 4-, 6- or 7-positions of the indole or indoline rings. Preferably R^7 is hydrogen.

Suitably the group $-(CR^{13}R^{14})_n-$ forms an ethylene or propylene group each of which can be substituted by C_{1-6}alkyl. The group $-(CR^{13}R^{14})_n-$ can be attached to the 4- or 6-position of the indole or indoline ring, preferably it is attached to the 6-position. Preferably the group $-(CR^{13}R^{14})_n-$ is ethylene.

Particularly preferred compounds of formula (I) include:

2,3-Dihydro-5-methyl-1-(3-nitrophenylcarbamoyl)-1H-pyrrolo [2,3-f]indole,

1-(3-Cyanophenylcarbamoyl)-2,3-dihydro-5-methyl-1H-pyrrolo[2,3-f]indole,

5-Methyl-1-(3-nitrophenylcarbamoyl)-2,3,6,7-tetrahydro-1H-pyrrolo[2,3-f]indole,

1-(3-Cyanophenylcarbamoyl)-5-methyl-2,3,6,7-tetrahydro-1H-pyrrolo[2,3-f]indole,

2,3-Dihydro-5-methyl-1-(3-trifluoromethylphenylcarbamoyl)-1H-pyrrolo[2,3-f]indole,

5-Methyl-1-(3-trifluoromethylphenylcarbamoyl)-2,3,6,7-tetrahydro-1H-pyrrolo[2,3-f]indole,

2,3-Dihydro-1-(3-ethoxycarbonylphenylcarbamoyl)-5-methyl-1H-pyrrolo[2,3-f]indole,

1-(3-Ethoxycarbonylphenylcarbamoyl)-5-methyl-2,3,6,7-tetrahydro-1H-pyrrolo[2,3-f]indole,
1-(3-Carbamoylphenylcarbamoyl)-2,3-dihydro-5-methyl-1H-pyrrolo[2,3-f]indole,
1-(3-Carbamoylphenylcarbamoyl)-5-methyl-2,3,6,7-tetrahydro-1H-pyrrolo[2,3-f]indole,
1-(3-Chlorophenylcarbamoyl)-2,3-dihydro-5-methyl-1H-pyrrolo[2,3-f]indole,
1-(3-Chlorophenylcarbamoyl)-5-methyl-2,3,6,7-tetrahydro-1H-pyrrolo[2,3-f]indole,
2,3-Dihydro-1-(3-methoxyphenylcarbamoyl)-5-methyl-1H-pyrrolo[2,3-f]indole,
1-(3-Methoxyphenylcarbamoyl)-5-methyl-2,3,6,7-tetrahydro-1H-pyrrolo[2,3-f]indole,
2,3-Dihydro-1-(3-dimethylaminophenylcarbamoyl)-5-methyl-1H-pyrrolo[2,3-f]indole,
or pharmaceutically acceptable salts thereof.

Certain compounds of the formula (I) can form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulphonic.

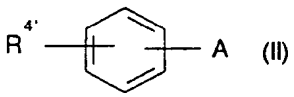
Compounds of formula (I) may also form solvates such as hydrates, and the invention also extends to these forms. When referred to herein, it is understood that the term 'compound of formula (I)' also includes these forms.

When R^1 (in an indole) and/or R^5 are hydrogen or when R^4 is hydroxy or NR^8R^9 and at least one of R^8 and R^9 are hydrogen the compounds of formula (I) may exist tautomerically in more than one form. The invention extends to these and any other tautomeric forms and mixtures thereof.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms including enantiomers and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis.

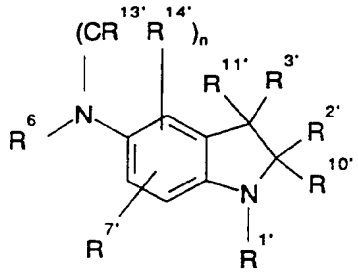
The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises

(a) the coupling of a compound of formula (II);



(II)

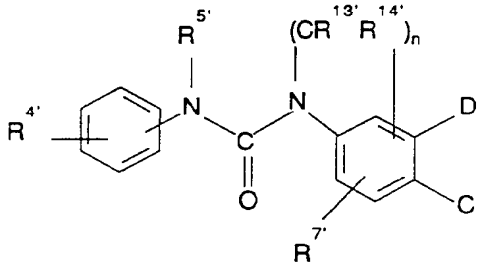
with a compound of formula (III);



(III)

wherein A and R^6 contain the appropriate functional group(s) necessary to form the moiety, $-NR^{5'}CO$ when coupled, wherein $R^{5'}$ is R^5 as defined in formula (I) or a group convertible thereto, n is as defined in formula (I), and the variables $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{10'}$, $R^{11'}$, $R^{13'}$, $R^{14'}$, $R^{4'}$ and $R^{7'}$ are R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4 and R^7 respectively, as defined in formula (I), or groups convertible thereto, and thereafter optionally and as necessary and in any appropriate order, converting any $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{10'}$, $R^{11'}$, $R^{13'}$, $R^{14'}$, $R^{4'}$, $R^{5'}$ and $R^{7'}$ when other than R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4, R^5, and R^7 respectively to R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4, R^5 and R^7, interconverting R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4, R^5 and R^7, and forming a pharmaceutically acceptable salt thereof;

or (b) cyclising a compound of formula (IV):



(IV)

wherein $R^{4'}$, $R^{5'}$, $R^{7'}$, $R^{13'}$, and $R^{14'}$ are as defined in formulae (II) and (III), n is as defined in formula (I), and C and D contain the appropriate functional group(s) necessary to form the indole or indoline ring substituted by $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{10'}$ and $R^{11'}$ as defined in formula (III), and thereafter optionally and as necessary in any appropriate order, converting any $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{10'}$, $R^{11'}$, $R^{13'}$, $R^{14'}$, $R^{4'}$, $R^{5'}$ and $R^{7'}$ when other than R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4, R^5 and R^7, to R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4, R^5 and R^7, interconverting R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4, R^5 and R^7, and forming a pharmaceutically acceptable salt.

Suitable examples of groups A and R^6 include:

(i) A is -N=C=O and R^6 is -H,

(ii) A is -$NR^{5'}$COL and R^6 is -H,

(iii) A is -$NHR^{5'}$ and R^6 is COL, or

wherein $R^{5'}$ is as defined above and L is a leaving group. Examples of suitable leaving groups L include imidazole, halogen such as chloro or bromo or phenoxy or phenylthio optionally substituted for example with halogen.

When A is -N=C=O and R^6 is H the reaction is suitably carried out in an inert solvent for example dichloromethane or toluene at ambient temperature.

When A is -$NR^{5'}$COL and R^6 is H or when A is -$NHR^{5'}$ and R^6 is COL, the reaction is suitably carried out in an inert solvent such as dichloromethane at ambient temperature optionally in the presence of a base, such as triethylamine or in dimethylformamide at ambient or elevated temperature.

The cyclisation of the compound of formula (IV) to prepare indoles (R^{10} and R^{11} are a bond) may be effected using standard methodology such as described in Comprehensive Heterocyclic Chemistry 1984 **4**, 313 **et. seq.** or J. Het. Chem. 1988 **25** p.1 **et seq.**

Examples of the more important routes include the Leimgruber synthesis, the Fischer synthesis, the Japp-Klingemann variation, the Madelung synthesis and the Nordlander synthesis.

Examples of the groups C and D in the preparation of indoles include:

(v) C is NO_2 and D is CH=CH-NZ_2 where each Z is independently C_{1-6} alkyl or together represent C_{2-7} alkylene;

(vi) C is $NR^{1'}$-N=C($R^{2'}$)-$CH_2R^{3'}$ and D is H;

(vii) C is NH-N=C(CO_2X)-$CH_2R^{3'}$ and D is H where X is C_{1-6} alkyl;

(viii) C is $NR^{1'}COR^{2'}$ and D is $CH_2R^{3'}$.

(ix) C is $NHCH_2CR^{3'}(OR)_2$ and D is H where R is a C_{1-6}alkyl group.

Indolines may also be prepared by reduction, e.g. with $NaCNBH_3$, of indoles produced by variants (vi) to (ix) above.

In reaction variant (v) (Leimgruber synthesis) the compound of formula (IV) is prepared from the 2-methylnitrophenyl urea by treatment with a dialkylacetal of the dialkylformamide $OHCNZ_2$ with heating and the product of formula (IV) cyclised by hydrogenation over a suitable catalyst such as palladium and charcoal optionally under pressure to yield the compound of formula (I) where R^1=R^2=R^3=H.

In reaction variant (vi) (Fischer synthesis) the compound of formula (IV) is prepared from the hydrazinophenyl urea by dehydration, preferably by heating, with the appropriate ketone $R^{2'}COCH_2R^{3'}$ and the product of formula (IV) cyclised by heating with an acid catalyst such as hydrochloric or sulphuric acid.

In reaction variant (vii) (Japp-Klingemann synthesis) the compound of formula (IV) is prepared from the aminophenyl urea by diazotisation followed by treatment for example with $CH_3COCH(CO_2X)$-$CH_2R^{3'}$ where X is C_{1-6} alkyl under basic conditions in aqueous alcohol as solvent.

The product of formula (IV) may then be cyclised as in the Fischer synthesis above.

In reaction variant (viii) (Madelung synthesis) the compound of formula (IV) is cyclised with base in an inert solvent optionally with heating.

In reaction variant (ix) (Nordlander synthesis), the compound of formula (IV) is cyclised by heating in a mixture of trifluoroacetic anhydride/acid.

It will be appreciated that when D is hydrogen, either or both indole isomers may be formed during the cyclisation process.

Suitable examples of groups $R^{2'}$, $R^{3'}$, $R^{4'}$, and $R^{7'}$ which are convertible to R^2, R^3, R^4, and R^7 alkyl groups respectively, include acyl groups which are introduced conventionally and may be converted to the corresponding alkyl group by conventional reduction, such as using sodium borohydride in an inert solvent followed by hydrogenolysis in an inert solvent. Hydrogen substituents may be obtained from alkoxycarbonyl groups which may be converted to hydrogen by hydrolysis and decarboxylation. When R^4 is hydroxy it is preferably protected in the compound of formula (II) as, for example, benzyl which is removed by hydrogenation.

Suitable examples of a group $R^{1'}$ which is convertible to R^1, include typical N-protecting groups such as alkoxycarbonyl, in particular t-butyloxycarbonyl, acetyl, trifluoroacetyl, benzyl and **para**-methoxybenzyl which are converted to R^1 hydrogen using conventional conditions.

Suitable examples of a group $R^{5'}$ which is convertible to R^5 include alkoxycarbonyl and benzyl or **para**-methoxybenzyl which are converted to R^5 is hydrogen using conventional conditions.

Interconversions of R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4, R^5 and R^7 are carried out by conventional procedures.

For example, in the case wherein R^1, R^2 and R^3 are C_{1-6} alkyl and R^5 is hydrogen it is possible to introduce a C_{1-6} alkyl group at the R^5 position by conventional alkylation using 1 molar equivalent of a C_{1-6} alkyl halide and 1 molar equivalent of a suitable base in an inert solvent. R^1 C_{1-6} alkyl groups may also be introduced by

conventional alkylation, for example using a C_{1-6} alkyl halide and base such as sodium hydride, or by reduction of C_{1-6} acyl.

R^4 halo and R^7 halo may be introduced by selective halogenation of the benzene ring or indole/indoline ring respectively using conventional conditions.

It should be appreciated that it may be necessary to protect any R^1 to R^{12} hydrogen variables which are not required to be interconverted.

Protection, especially of a $R^{1'}$ hydrogen, may also be necessary during coupling reaction (a) and ring-forming reaction (b) above.

Suitable protecting groups and methods for their attachment and removal are conventional in the art of organic chemistry, such as those described in Greene T.W. 'Protective groups in organic synthesis' New York, Wiley (1981).

It is preferable, however, to introduce and interconvert the groups R^1 to R^{12} before coupling compounds of formulae (II) and (III) together, or cyclising the compound of formula (IV).

Compounds of formula (I) which are substituted indoles, and their appropriate derivatives, can be converted to the corresponding indolines, and vice versa, by conventional methods, e.g. reduction with $NaCNBH_3$ in acetic acid and oxidation using MnO_2 in an inert solvent.

Compounds of formula (II) in which A is $NHR^{5'}$ are known compounds or can be prepared analogously to known compounds, see, for example, WO 92/05170.

Compounds of formula (II) in which A is -N=C=O may be prepared by treating a compound of formula (II) in which :

i) A is amino, with phosgene or a phosgene equivalent, in the presence of excess base in an inert solvent.

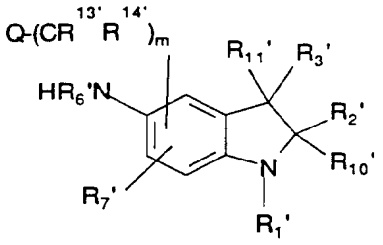
ii) A is acylazide (i.e. CON_3), via the nitrene, by thermal rearrangement using conventional conditions (ref L.S. Trifonov **et al**, Helv. Chim. Acta 1987 **70** 262).

iii) A is $CONH_2$, via the nitrene intermediate using conventional conditions.

Compounds of formula (II) in which A is $-NR^{5'}COL$ may be prepared by reacting a compound of formula (II) in which A is $-NHR^{5'}$ with phosgene or a phosgene equivalent, in an inert solvent, at low temperature, if necessary in the presence of one equivalent of a base such as triethylamine.

Compounds of formula (III) may be prepared:

(a) by cyclisation of compounds of formula (V), followed by reduction to the amine if necessary

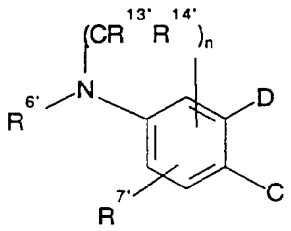


(V)

wherein Q is $CR^{13}R^{14}L$, $CR^{13}O$ or CO_2R where L is a leaving group and R^{13} and R^{14} are as defined in formula (I), m is 1 or 2, $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{7'}$, $R^{10'}$, $R^{11'}$, $R^{13'}$ and $R^{14'}$ are as defined in formula (III) above, $R^{6'}$ is a group R^6 as defined in formula (III) and R is an aryl or

C_{1-6}alkyl group,

or (b) cyclisation of compounds of formula (VI)



(VI)

wherein , $R^{6'}$, $R^{7'}$, $R^{13'}$, $R^{14'}$ and n are as defined in formula (V) and C and D are as defined in formula (IV) above.

The cyclisation of a compound of formula (V) may be suitably carried out in an inert solvent at ambient or elevated temperatures, optionally in the presence of a base. Reduction may be carried out using conventional reduction techniques. The cyclisation of a compound of formula (VI) may be suitably carried out using the procedures outlined for the cyclisation of a compound of formula (IV), above.

Compounds of formula (II) in which A is halogen and $R^{4'}$ is hydrogen are commercially available.

Novel intermediates of formulae (III) and (IV) also form part of the invention.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative. N-oxides may be formed conventionally by reaction with hydrogen peroxide or percarboxylic acids.

Compounds of formula (I) and their pharmaceutically acceptable salts have $5HT_{2C}$ receptor antagonist activity, and certain compounds are potential $5HT_{2B}$ antagonists. Compounds of the invention are believed to be of potential use in the treatment of CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive

disorders, migraine, Alzheimers disease, sleep disorders, feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of certain GI disorders such as IBS as well as microvascular diseases such as macular oedema and retinopathy.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of the above disorders.

The invention further provides a method of treatment or prophylaxis of the above disorders, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis the above disorders.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either

suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 70.0 mg, for example 0.2 to 5 mg; and such unit doses may be administered more than once a day, for example two or three a day, so that the total daily dosage is in the range of about 0.01 to 100 mg; and such therapy may extend for a number of weeks or months.

When administered in accordance with the invention, no unacceptable toxicological effects are expected with the compounds of the invention.

The following Examples illustrate the preparation of compounds of the invention.

Description 1

1-Acetyl-5-aminoindoline (D1)

1-Acetyl-5-nitroindoline (12.77g, 62 mmol), cyclohexene (62 ml, 610 mmol), and 5% palladium on charcoal (2.34g) were stirred at reflux under nitrogen for 18h. A further portion of catalyst (0.5g) was then added, and reflux was continued for a further 3h. The mixture was cooled, filtered through Kieselguhr, and evaporated to give the title compound (9.33g, 85%) as an orange-yellow solid.

NMR (D_6-DMSO) δ: 2.05 (3H, s), 3.0 (2H, t, J 8), 3.97 (2H, t, J 8), 4.97 (2H, bs), 6.33 (1H, dd, J 7,1), 6.46 (1H, d, J 1), 7.72 (1H, d, J 7).

Description 2

N-(1-Acetyl-5-indolinyl)-2,2-diethoxyethylamine (D2)

1-Acetyl-5-aminoindoline (D1) (9.33g, 53 mmol), bromoacetaldehyde diethyl acetal (6.0 ml, 40 mmol) and sodium hydrogen carbonate (4.58g, 54 mmol) was stirred at reflux under nitrogen for 64h. Further acetal (2.0 ml, 13 mmol) was then added, and reflux was continued for a further 24h. The mixture was cooled, filtered, and evaporated to near-dryness. Chromatography on silica gel using ethyl acetate/petroleum ether (b.p. 60-80°C) (50-100% ethyl acetate) gave the title compound (6.59g) as a yellow-brown solid, in addition to recovered starting amine (3.09g). The yield of product was 63%, based on consumed starting material.

NMR ($CDCl_3$) δ: 1.25 (6H, t, J 7), 2.2 (3H, s), 3.13 (2H, t, J 8), 3.22 (2H, d, J 5), 3.5-3.65 (2H, m), 3.65-3.8 (2H, m), 4.01 (2H, t, J 8), 4.68 (1H, t, J 5), 6.5 (2H, m), 8.03 (1H, d, J 7).

Alternative Procedure

1-Acetyl-5-aminoindoline (D1) was reductively alkylated with glyoxal monomethyl acetal in ethanol at 45°C using 10% palladium on charcoal and hydrogen at 50 p.s.i. Removal of the catalyst by filtration followed by evaporation of the solvent afforded the corresponding dimethyl acetal which was used directly in Description 3 instead of the diethyl acetal.

Description 3

1-Acetyl-5-trifluoroacetyl-2,3-dihydropyrrolo[2,3-f]indole (D3)

N-(1-Acetyl-5-indolinyl)-2,2-diethoxyethylamine (D2) (6.51g, 22 mmol) was added to an ice-cold, stirred mixture of trifluoroacetic acid (25 ml) and trifluoroacetic anhydride (25 ml). The mixture was stirred at 0°C under nitrogen for 0.5h, after which time further trifluoroacetic acid (40 ml) was added. The mixture was then heated at reflux for 64h, cooled, and evaporated to dryness. Chromatography on silica gel using ethyl acetate/chloroform (0-60% ethyl acetate) then gave the title compound (6.28, 89%) as a light cream solid which darkened slightly on standing.

NMR ($CDCl_3$) δ: 2.33 (3H, s), 3.37 (2H, t, J 8), 4.17 (2H, t, J 7), 6.76 (1H, d, J 3), 7.45 (1H, m), 8.27 (1H, s), 8.44 (1H, s).

Description 4

1-Acetyl-2,3-dihydropyrrolo[2,3-f]indole (D4)

1-Acetyl-5-trifluoroacetyl-2,3-dihydropyrrolo[2,3-f]indole (D3) (2.80g, 9.4 mmol) was suspended with stirring in methanol (100 ml), and anhydrous potassium carbonate (1.96g, 14.2 mmol) was added. The mixture was stirred for 0.5h, evaporated to near-dryness, and partitioned between ethyl acetate and water. After separation, the aqueous portion was extracted with 5% methanol/chloroform, and the combined organics were dried (Na_2SO_4), filtered and evaporated, giving the title compound (1.53g, 80%) as a cream solid.

NMR (D_6-DMSO) δ: 2.15 (3H, s), 3.18 (2H, t, J 8), 4.08 (2H, t, J 8), 6.33 (1H, bs), 7.2 (2H, m), 8.22 (1H, s), 10.9 (1H, bs).

Description 5

1-Acetyl-5-methyl-2,3-dihydropyrrolo[2,3-f]indole (D5)

Sodium hydride (80%, 0.25g, 8.3 mmol) was stirred under nitrogen in dry N,N-dimethylformamide (DMF) (5 ml), as 1-acetyl-2,3-dihydropyrrolo[2,3-f]indole (D4) (1.52g, 7.6 mmol) was added in DMF (20 ml), with effervescence. The mixture was stirred for 0.5h, and iodomethane (0.52 ml, 8.3 mmol) was then added in DMF (5 ml). After stirring for a further 1h, excess sodium hydride was quenched by addition of water (1 ml), and the mixture was partitioned between ethyl acetate and water, and separated. The organic portion was washed with water and brine, dried (Na_2SO_4) and evaporated.

Chromatography on silica gel using ethyl acetate/chloroform (0-50% ethyl acetate) then gave the title compound (0.80g, 49%) as a pale yellow solid.

NMR ($CDCl_3$) ca.5:1 mixture of rotamers δ: 2.26 (major, 3H, s), 2.51 (minor, 3H, s), 3.16 (minor, 2H, t, J 8), 3.3 (major, 2H, t, J 8), 3.74 (major, 3H, s), 3.77 (minor, 3H, s), 4.1 (major, 2H, t, J 8), 4.19 (minor, 2H, t, J 8), 6.44 (both, 1H, d, J 2), 6.98 (major, 1H, d, J 2), 7.0 (minor, m), 7.09 (major, 1H, s), 7.18 (minor, 1H, s), 7.31 (minor, 1H, s), 8.48 (major, 1H, s).

Description 6

5-Methyl-2,3-dihydropyrrolo[2,3-f]indole (D6)

1-Acetyl-5-methyl-2,3-dihydropyrrolo[2,3-f]indole (D5) (0.70g, 3.3 mmol) was stirred at reflux under nitrogen in 10% sodium hydroxide solution (50 ml) for 4h. The mixture was cooled, diluted with water (200 ml), and extracted with ethyl acetate. The extract was dried (Na_2SO_4) and evaporated to give the title compound (0.58g) as a light brown gum, still containing ca. 20% of the starting amide (NMR). This material was used in the next step without purification.

NMR ($CDCl_3$) δ: 3.12 (2H, t, J 9), 3.33 (1H, bs), 3.56 (2H, t, J 9), 3.7 (3H, s), 6.27 (1H, d, J 3), 6.85 (1H, s), 6.9 (1H, d, J 3), 7.08 (1H, s).

Example 1

2,3-Dihydro-5-methyl-1-(3-nitrophenylcarbamoyl)-1H-pyrrolo [2,3-f]indole (E1)

To a solution of 1,1'-carbonyldiimidazole (0.36g, 2.2mmol) in dry dichloromethane (10 ml) at 0°C was added 3-nitroaniline (0.304g, 2.2 mmol) and triethylamine (0.31ml, 2.2 mmol) in dichloromethane (10 ml). After stirring at 0°C for 1 h the mixture was evaporated *in vacuo*. To the residue was added dry DMF (10 ml) and a solution of 2,3-dihydro-5-methyl-1H-pyrrolo[2,3-f] indole (D6, 0.38g, 2.2 mmol) in DMF (5 ml). The mixture was heated at 120°C for 1 h, then cooled and poured into water. The precipitate was filtered off, washed with water and dried. Crude product was chromatographed on silica gel eluted with 2-3% methanol/dichloromethane to give the title compound (0.5g, 76%), m.p. 228-231°C.

NMR (d_6-DMSO) δ : 3.28 (2H, t, J = 7), 3.74 (3H, s), 4.18 (2H, t, J = 7), 6.32 (1H, d, J = 2), 7.20 (1H, d, J = 2), 7.27 (1H, s), 7.58 (1H, t, J = 8), 7.85 (1H, d, J = 8), 8.04 (1H, d, J = 8), 8.07 (1H, s), 8.62 (1H, s), 8.93 (1H, s).

MS (CI) m/e 337 (MH^+)

Example 2

1-(3-Cyanophenylcarbamoyl)-2,3-dihydro-5-methyl-1H-pyrrolo[2,3-f]indole (E2)

The title compound was prepared by the procedure of Example 1, starting with 3-aminobenzonitrile (0.26g, 2.2 mmol), carbonyldiimidazole (0.36g, 2.2 mmol), triethylamine (0.31 ml, 2.2 mmol) and pyrrolo [2,3-f]indole. (D6, 0.38g, 2.2 mmol). Chromatography as before gave the title compound (0.28g, 40%), m.p. 199-200° C.

NMR (d_6-DMSO) δ: 3.28 (2H, t, J = 7), 3.73 (3H, s), 4.18 (2H, t, J = 7), 6.32 (1H, d, J = 2), 7.20 (1H, d, J = 2), 7.27 (1H, s), 7.44 (1H, d, J = 7), 7.51 (1H, t, J = 7), 7.90 (1H, d, J = 7), 8.05 (1H, s), 8.08 (1H, s), 8.79 (1H, s)

MS (EI) m/e 316 (M^+)

Example 3

5-Methyl-1-(3-nitrophenylcarbamoyl)-2,3,6,7-tetrahydro-1H-pyrrolo[2,3-f]indole (E3)

To a suspension of the nitrophenyl pyrroloindole (E1, 0.42g, 1.25 mmol) in glacial acetic acid (10 ml) was added sodium cyanoborohydride (79 mg, 1.25 mmol). The mixture was stirred for 1h at room temperature, then diluted with water, basified with 40% sodium hydroxide and extracted with dichloromethane. The organic extract was washed with water, dried and evaporated. The crude product was chromatographed on silica gel eluted with 2% methanol/dichloromethane. Eluted material was recrystallised twice from dichloromethane/methanol/petrol to give the title compound (0.22g, 52%), m.p. 187-189° C.

NMR (d_6-DMSO) δ : 2.65 (3H, s), 2.82 (2H, m), 3.10 (2H, m), 3.19 (2H, m), 4.11 (2H, m), 6.45 (1H, s), 7.55 (1H, t, J = 7), 7.69 (1H, s), 7.82 (1H, d, J = 7), 8.00 (1H, d, J = 7), 8.50 (1H, s), 8.85 (1H, s).

MS (CI) m/e 339 (MH^+)

Example 4

1-(3-Cyanophenylcarbamoyl)-5-methyl-2,3,6,7-tetrahydro-1H-pyrrolo[2,3-f]indole (E4)

The cyanophenyl pyrrolo indole (E2, 0.28g, 0.89 mmol) was reduced with sodium cyanoborohydride (57 mg, 0.9 mmol) in glacial acetic acid (10 ml) according to the procedure of Example 3. After chromatography, recrystallisation from dichloromethane/petrol gave the title compound (0.21g, 74%), m.p. 178-180° C.

NMR (d_6-DMSO) δ : 2.64 (3H, s), 2.80 (2H, t, J = 7), 3.08 (2H, t, J = 7), 3.18 (2H, t, J = 7), 4.08 (2H, t, J = 7), 6.43 (1H, s), 7.45 (2H, m, J = 7), 7.67 (1H, s), 7.86 (1H, d, J = 7), 8.04 (1H, s), 8.49 (1H, s)

Found: C, 70.80; H, 5.79; N, 17.24%
$C_{18}H_{18}N_4O.¼H_2O$ requires C, 70.67; H, 5.77; N, 17.35%

Example 5

2,3-Dihydro-5-methyl-1-(3-trifluoromethylphenylcarbamoyl)-1H-pyrrolo[2,3-f]indole (E5)

The title compound was prepared in 55% yield from 2,3-dihydro-5-methyl-1H-pyrrolo[2,3-f]indole (D6) and3-trifluoromethylphenyl isocyanate.

NMR (D_6 DMSO) δ : 3.27 (2H, t, J = 7), 3.73 (3H, s), 4.18 (2H, t, J = 7), 6.31 (1H, d, J = 2), 7.19 (1H, d, J = 2), 7.27 (1H, s), 7.32 (1H, d, J = 8), 7.52 (1H, m), 7.88 (1H, d, J = 8), 8.07 (1H, s), 8.79 (1H, s)

Example 6

5-Methyl-1-(3-trifluoromethylphenylcarbamoyl)-2,3,6,7-tetrahydro-1H-pyrrolo[2,3-f]indole hydrogen maleate (E6)

The title compound was prepared in 85% yield from the indole E5 using a procedure similar to that for E3 followed by salt formation using maleic acid, m.p. 160°C (dec.).

NMR (D_6-DMSO) δ : 2.67 (3H, s), 2.83 (2H, t, J = 7), 3.09 (2H, t, J = 7), 3.23 (2H, t, J = 7), 4.10 (2H, t, J = 7), 6.26 (2H, s), 6.52 (1H, s), 7.31 (1H, d, J = 8), 7.50 (1H, m), 7.69 (1H, s), 7.83 (1H, d, J = 8), 8.03 (1H, s), 8.70 (1H, s).

Found: M^+ 361, $C_{19}H_{18}N_3OF_3$ requires 361

Example 7

2,3-Dihydro-1-(3-ethoxycarbonylphenylcarbamoyl)-5-methyl-1H-pyrrolo[2,3-f]indole (E7)

The title compound was prepared by the procedure of Example 1, starting with ethyl 3-aminobenzoate (0.375g, 2.3 mmol), carbonyldiimidazole (0.38g, 2.3 mmol), triethylamine (0.32 ml, 2.3 mmol) and pyrrolo[2,3-f]indole (D6, 0.39g, 2.3 mmol). Crude product was recrystallised from dichloromethane/petrol to give the title compound (0.55g, 66%) m.p. 190-191° C

NMR (d_6-DMSO) δ: 1.34 (3H, t, J = 7), 3.27 (2H, t, J = 8), 3.73 (3H, s), 4.18 (2H, t, J = 8), 4.34 (2H, q, J = 7), 6.32 (1H, d, J = 3), 7.19 (1H, d, J = 3), 7.28 (1H, s), 7.45 (1H, t, J = 8), 7.60 (1H, d, J = 8), 7.91 (1H, d, J = 8), 8.05 (1H, s), 8.24 (1H, s), 8.69 (1H, s)

MS (CI) m/e 364 (MH^+)

Example 8

1-(3-Ethoxycarbonylphenylcarbamoyl)-5-methyl-2,3,6,7-tetrahydro-1H-pyrrolo[2,3-f]indole (E8)

The ethoxycarbonyl compound (E7, 0.43g, 1.2 mmol) was reduced with sodium cyanoborohydride (76 mg, 1.2 mmol) in acetic acid (10 ml) according to the procedure of

Example 3. After chromatography, recrystallisation from dichloromethane/petrol gave the title compound (0.27g, 62%), m.p. 153-154° C.

NMR (d_6-DMSO) δ: 1.34 (3H, t, J = 7), 2.64 (3H, s), 2.81 (2H, m), 3.08 (2H, m), 3.18 (2H, m), 4.01 (2H, m), 4.32 (2H, q, J = 7), 6.43 (1H, s), 7.41 (1H, t, J = 8), 7.58 (1H, d, J = 8), 7.68 (1H, s), 7.88 (1H, d, J = 8), 8.20 (1H, s), 8.60 (1H, s).

Found: C, 68.58; H, 6.36; N, 11.64%
$C_{21}H_{23}N_3O_3$ requires C, 69.02; H, 6.34; N, 11.50%

Example 9
1-(3-Carbamoylphenylcarbamoyl)-2,3-dihydro-5-methyl-1H-pyrrolo[2,3-f]indole (E9)

The title compound was prepared by the procedure of Example 1, starting with 3-aminobenzamide (0.30g, 2.2 mmol), carbonyldiimidazole (0.36g, 2.2 mmol), triethylamine (0.31 ml, 2.2 mmol) and pyrrolo [2,3-f]indole (D6, 0.38g, 2.2 mmol). Recrystallisation from dichloromethane/methanol gave the title compound (0.29, 39%), m.p. 230-235° C.

NMR (d_6-DMSO) δ: 3.25 (2H, t, J = 8), 3.72 (3H, s), 4.16 (2H, t, J = 8), 6.30 (1H, d, J = 3), 7.18 (1H, d, J = 3), 7.25 (1H, s), 7.32 (1H, s), 7.35 (1H, t, J = 8), 7.50 (1H, d, J = 8), 7.77 (1H, d, J = 8), 7.91 (1H, s), 8.04 (2H, s), 8.59 (1H, s).

MS (CI) m/e 335 (MH^+)

Example 10
1-(3-Carbamoylphenylcarbamoyl)-5-methyl-2,3,6,7-tetrahydro-1H-pyrrolo[2,3-f]indole (E10)

The carbamoyl compound (E9, 0.28g, 0.84 mmol), was reduced with sodium cyanoborohydride (54 mg, 0.85 mmol) in acetic acid (10 ml) according to the procedure of Example 3. Recrystallisation from dichloromethane/methanol gave the title compound (0.23g, 81%), m.p. 206-210° C.

NMR (d_6-DMSO) δ: 2.62 (3H, s), 2.80 (2H, t, J = 8), 3.08 (2H, t, J = 8), 3.18 (2H, t, J = 8), 4.09 (2H, t, J = 8), 6.43 (1H, s), 7.33 (1H, s + 1H, t, J = 8), 7.49 (1H, d, J = 8), 7.49 (1H, d, J = 8), 7.68 (1H, s), 7.74 (1H, d, J = 8), 7.91 (1H, s), 8.02 (1H, s), 8.50 (1H, s).

Found: C, 67.15; H, 6.08; N, 16.42%
$C_{19}H_{20}N_4O_2$ requires C, 67.84; H, 5.99; N, 16.65%

Example 11

1-(3-Chlorophenylcarbamoyl)-2,3-dihydro-5-methyl-1H-pyrrolo[2,3-f]indole (E11)

The title compound was prepared by the procedure of Example 1, starting with 3-chloroaniline (0.28g, 2.2 mmol), carbonyldiimidazole (0.36g, 2.2 mmol) and pyrrolo[2,3-f]indole (D6, 0.38g, 2.2 mmol), with no triethylamine. Chromatography in 2% methanol/dichloromethane and recrystallisation from methanol gave the title compound (0.44g, 61%), m.p. 156-167° C.

NMR (d_6-DMSO) δ: 3.28 (2H, t, J = 8), 3.73 (3H, s), 4.18 (2H, t, J = 8), 6.32 (1H, d, J = 3), 7.05 (1H, d, J = 8), 7.21 (1H, d, J = 3), 7.29 (1H, s), 7.35 (1H, d, J = 8), 7.57 (1H, d, J = 8), 7.80 (1H, s), 8.05 (1H, s), 8.62 (1H, s).

MS (CI) m/e 326 (MH^+)

Example 12

1-(3-Chlorophenylcarbamoyl)-5-methyl-2,3,6,7-tetrahydro-1H-pyrrolo[2,3-f]indole (E12)

The chloro compound (E11, 0.35g, 1.07 mmol) was reduced with sodium cyanoborohydride (68 mg, 1.07 mmol) in acetic acid (10 ml) according to the procedure of Example 3. Chromatography in 2% methanol/dichloromethane and recrystallisation from methanol/water gave the title compound (0.26g, 74%), m.p. 146-147° C.

NMR (d_6-DMSO) δ: 2.64 (3H, s), 2.81 (2H, t, J = 8), 3.08 (2H, t, J = 8), 3.18 (2H, t, J = 8), 6.94 (1H, s), 7.02 (1H, d, J = 8), 7.29 (1H, t, J = 8), 7.50 (1H, d, J = 8), 7.67 (1H, s), 7.76 (1H, s), 8.52 (1H, s).

Found: C, 65.84; H, 5.55; N, 12.72%
$C_{18}N_{18}H_3Cl$ requires C, 65.95; H, 5.53; N, 12.82%

Example 13
2,3-Dihydro-1-(3-methoxyphenylcarbamoyl)-5-methyl-1H-pyrrolo[2,3-f]indole (E13)

A solution of 3-methoxyphenyl isocyanate (0.08 ml, 0.6 mmol) and pyrrolo [2,3-f]indole (D6, 0.10g, 0.58 mmol) in dry dichloromethane (5 ml) was stirred overnight at room temperature. Evaporation of solvent gave the title compound.

NMR ($CDCl_3$) δ: 3.28 (2H, t, J = 8), 3.74 (3H, s), 3.83 (3H, s), 4.13 (2H, t, J = 8), 6.42 (1H, d, J = 3), 6.63 (1H, d, J = 8), 6.69 (1H, s), 6.93 (1H, d, J = 8), 6.99 (1H, d, J = 3), 7.13 (1H, s), 7.22 (1H, t, J = 8), 7.27 (2H, s), 7.94 (1H, s).

MS (CI) m/e 322 (MH^+)

Example 14
1-(3-Methoxyphenylcarbamoyl)-5-methyl-2,3,6,7-tetrahydro-1H-pyrrolo[2,3-f]indole (E14)

The methoxy compound (E13) was reduced with sodium cyanoborohydride in acetic acid according to the procedure of Example 3. Chromatography in 2% methanol/dichloromethane and recrystallisation from dichloromethane/petrol gave the title compound, m.p. 152-154° C.

NMR ($CDCl_3/CD_3OD$) δ: 2.72 (3H, s), 2.91 (2H, t, J = 8), 3.13 (2H, t, J = 8), 3.27 (2H, t, J = 8), 3.82 (3H, s), 4.05 (2H, t, J = 8), 6.39 (1H, s), 6.53 (1H, broad s), 6.61 (1H, d, J = 8), 6.91 (1H, d, J = 8), 7.20 (1H, s + 1H, t, J = 8), 7.68 (1H, s).

MS (EI) m/e 323 (M^+)

Example 15

2,3-Dihydro-1-(3-dimethylaminophenylcarbamoyl)-5-methyl-1H-pyrrolo[2,3-f]indole (E15)

The title compound was prepared by the procedure of Example 1, starting with N,N-dimethyl-1,3-phenylenediamine dihydrochloride (0.46g, 2.2 mmol), carbonyldiimidazole (0.36g, 2.2 mmol), triethylamine (0.62 ml, 4.4 mmol) and pyrrolo [2,3-f]indole (D6, 0.38g, 2.2 mmol). Chromatography in 2% methanol/dichloromethane and recrystallisation from dichloromethane/petrol gave the title compound (0.24g, 33%), m.p. 167-170° C.

NMR (d_6-DMSO)δ: 2.89 (6H, s), 3.25 (2H, t, J = 8), 3.72 (3H, s), 4.13 (2H, t, J = 8), 6.32 (1H, d, J = 3), 6.40 (1H, d, J = 8), 6.96 (1H, d, J = 8), 7.04 (1H, s), 7.09 (1H, t, J = 8), 7.18 (1H, d, J = 3), 7.25 (1H, s), 8.05 (1H, s), 8.22 (1H, s).

Found: C, 71.16; H, 6.66; N, 16.49%

$C_{20}H_{22}N_4O$ requires C, 71.83; H, 6.63; N, 16.75%

Pharmacological Data

[^{3}H]-mesulergine binding to rat or human 5-HT$_{2C}$ clones expressed in 293 cells in vitro

Evidence from the literature suggests that 5-HT$_{2C}$ antagonists may have a number of therapeutic indications including the treatment of anxiety, migraine, depression, feeding disorders and obsessive compulsion disorders. (Curzon and Kennett, 1990; Fozard and Gray, 1989) and Alzheimer's Disease (Lawlor, 1989, J. Arch. Gen. Psychiat. Vol. 46 p.542).

The affinity of test drugs for the 5-HT$_{2C}$ binding site can be determined by assessing their ability to displace [^{3}H]-mesulergine from 5-HT$_{2C}$ clones expressed in 293 cells (Julius *et al.*, 1988). The method employed was similar to that of Pazos et al, 1984.

The cells suspension (400ml) was incubated with [^{3}H]-mesulergine (0.5nM) in Tris HCl buffer (pH 7.4) at 37°C for 30 minutes. Non-specific binding was measured in the presence of mianserin (10^{-6}M). Ten concentrations of test drug (3×10^{-9} to 10^{-4}M final concentration) were added in a volume of 50ml. The total assay volume was 500ml. Incubation was stopped by rapid filtration using a Brandel cell harvester and radioactivity measured by scintillation counting. The IC_{50} values were determined using a four parameter logistic program (DeLean 1978) and the pK_i (the negative logarithm of the inhibition constant) calculated from the Cheng Prusoff equation where:

$$K_i = \frac{IC_{50}}{1 + \frac{C}{Kd}}$$

K_i = inhibition constant.

C = concentration of [^{3}H]-mesulergine

Kd = Affinity of mesulergine for 5-HT$_{2C}$ binding sites.

Curzon, G.A. and Kennett, G.A. (1990). TIPS, Vol. 11, 181-182.

Fozard, J.R. and Gray, J.A. (1989). TIPS, Vol. 10, 307-309.

Pazos, A. *et al.* (1984). Eur. J. Pharmacol., 106, 531-538.

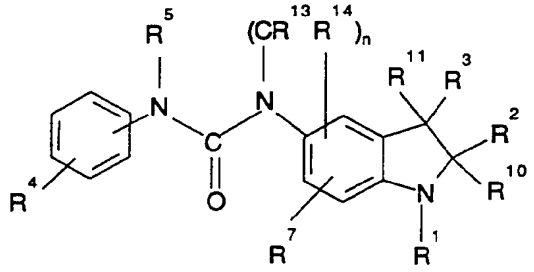
Julius *et al.* (1988) Science 241, 558-564

DeLean A, Munson P.J., Rodbaud D (1978) Am. J. Physiol 235, E97-E102.

Results: The compounds of examples 3, 4, 6, 8, 10 , 12, 14 and 15 had pK_i values in the range 6.7 to 7.6.

Claims:

1. A compound of formula (I) or a salt thereof:



(I)

wherein:

R^1 is hydrogen or C_{1-6} alkyl;

R^2, R^3, R^{10} and R^{11} are independently hydrogen or C_{1-6} alkyl, or R^{10} and R^{11} together form a bond, or R^2 and R^{10} or R^3 and R^{11} together form a C_{2-6} alkylene chain;

R^4 is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, halogen, nitro, trifluoromethyl, cyano, CO_2R^{12} or $CONR^{15}R^{16}$ where R^{12}, R^{15} and R^{16} are independently hydrogen or C_{1-6} alkyl, $S(O)_nR^{17}$ or $S(O)_nNR^{18}R^{19}$ where n is 1 or 2 and R^{17}, R^{18} and R^{19} are independently hydrogen or C_{1-6} alkyl;

R^5 is hydrogen or C_{1-6} alkyl;

R^7 is hydrogen, C_{1-6} alkyl, OR^{12} or halogen, where R^{12} is hydrogen or C_{1-6} alkyl; and n is 2 or 3; and

the groups R^{13} and R^{14} are independently hydrogen or C_{1-6} alkyl.

2. A compound according to claim 1 in which R^1 is C_{1-6}alkyl.

3. A compound according to claim 2 in which R^2 and R^3 are hydrogen.

4. A compound according to claim 3 in which R^4 is nitro, cyano, halo, carbamoyl, C_{1-6}alkoxy or trifluoromethyl.

5. A compound according to claim 4 in which R^5 and R^7 are hydrogen.

6. A compound according to claim 5 in which $(CHR^{13})_n$ is an ethylene group.

7. A compound according to claim 1 which is selected from:

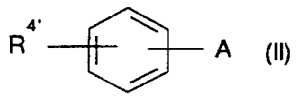
2,3-Dihydro-5-methyl-1-(3-nitrophenylcarbamoyl)-1H-pyrrolo [2,3-f]indole,
1-(3-Cyanophenylcarbamoyl)-2,3-dihydro-5-methyl-1H-pyrrolo[2,3-f]indole,
5-Methyl-1-(3-nitrophenylcarbamoyl)-2,3,6,7-tetrahydro-1H-pyrrolo[2,3-f]indole,
1-(3-Cyanophenylcarbamoyl)-5-methyl-2,3,6,7-tetrahydro-1H-pyrrolo[2,3-f]indole,
2,3-Dihydro-5-methyl-1-(3-trifluoromethylphenylcarbamoyl)-1H-pyrrolo[2,3-f]indole,
5-Methyl-1-(3-trifluoromethylphenylcarbamoyl)-2,3,6,7-tetrahydro-1H-pyrrolo[2,3-f]indole,
2,3-Dihydro-1-(3-ethoxycarbonylphenylcarbamoyl)-5-methyl-1H-pyrrolo[2,3-f]indole,
1-(3-Ethoxycarbonylphenylcarbamoyl)-5-methyl-2,3,6,7-tetrahydro-1H-pyrrolo[2,3-f]indole,
1-(3-Carbamoylphenylcarbamoyl)-2,3-dihydro-5-methyl-1H-pyrrolo[2,3-f]indole,
1-(3-Carbamoylphenylcarbamoyl)-5-methyl-2,3,6,7-tetrahydro-1H-pyrrolo[2,3-f]indole,
1-(3-Chlorophenylcarbamoyl)-2,3-dihydro-5-methyl-1H-pyrrolo[2,3-f]indole,
1-(3-Chlorophenylcarbamoyl)-5-methyl-2,3,6,7-tetrahydro-1H-pyrrolo[2,3-f]indole,
2,3-Dihydro-1-(3-methoxyphenylcarbamoyl)-5-methyl-1H-pyrrolo[2,3-f]indole,
1-(3-Methoxyphenylcarbamoyl)-5-methyl-2,3,6,7-tetrahydro-1H-pyrrolo[2,3-f]indole,
2,3-Dihydro-1-(3-dimethylaminophenylcarbamoyl)-5-methyl-1H-pyrrolo[2,3-f]indole,
or a pharmaceutically acceptable salt thereof.

8. A compound according to any one of claims 1 to 7 for use in therapy.

9. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 7 and a pharmaceutically acceptable carrier or excipient.

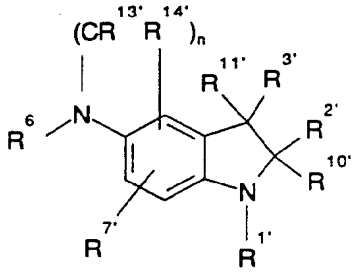
10. A process for the preparation of a compound of formula (I) or a salt thereof, which process comprises:

(a) the coupling of a compound of formula (II);



(II)

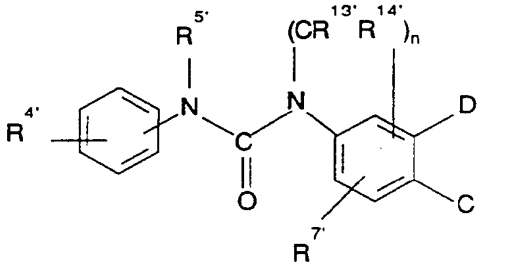
with a compound of formula (III);



(III)

wherein A and R^6 contain the appropriate functional group(s) necessary to form the moiety, $-NR^{5'}CO$ when coupled, wherein $R^{5'}$ is R^5 as defined in formula (I) or a group convertible thereto, n is as defined in formula (I), and the variables $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{10'}$, $R^{11'}$, $R^{13'}$, $R^{14'}$, $R^{4'}$ and $R^{7'}$ are R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4 and R^7 respectively, as defined in formula (I), or groups convertible thereto, and thereafter optionally and as necessary and in any appropriate order, converting any $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{10'}$, $R^{11'}$, $R^{13'}$, $R^{14'}$, $R^{4'}$, $R^{5'}$ and $R^{7'}$ when other than R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4, R^5, and R^7 respectively to R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4, R^5 and R^7, interconverting R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4, R^5 and R^7, and forming a pharmaceutically acceptable salt thereof;

or (b) cyclising a compound of formula (IV):



(IV)

wherein $R^{4'}$, $R^{5'}$, $R^{7'}$, $R^{13'}$, and $R^{14'}$ are as defined in formulae (II) and (III), n is as defined in formula (I), and C and D contain the appropriate functional group(s) necessary to form the indole or indoline ring substituted by $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{10'}$ and $R^{11'}$ as defined in formula (III), and thereafter optionally and as necessary in any appropriate order, converting any $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{10'}$, $R^{11'}$, $R^{13'}$, $R^{14'}$, $R^{4'}$, $R^{5'}$ and $R^{7'}$ when other than R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4, R^5 and R^7, to R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4, R^5 and R^7, interconverting R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4, R^5 and R^7, and forming a pharmaceutically acceptable salt.

INTERNATIONAL SEARCH REPORT

Inten al Application No
PCT/EP 95/00427

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D487/04 A61K31/40 C07D471/04 C07D487/10 C07D471/10
//(C07D487/04,209:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOURNAL OF MEDICINAL CHEMISTRY, vol. 29,no. 111, 1986 WASHINGTON US, pages 2415-2418, P. FLUDZINSKI ET AL. '2,3-Dialkyl(dimethylamino)indoles: Interaction with 5HT1, 5HT", and rat stomach fundal serotonin receptors' see table II ---	1,9
A	WO,A,92 05170 (BEECHAM) 2 April 1992 cited in the application see page 11, line 24 - page 12, line 2; claim 1 ---	1,9
P,A	WO,A,94 04533 (SMITHKLINE BEECHAM) 3 March 1994 see page 9, line 15 - line 21; claim 1 -----	1,9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
11 May 1995	23. 05. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

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INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/EP 95/00427

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		CA-A-	2091246	14-03-92
		EP-A-	0550507	14-07-93
		JP-T-	6500551	20-01-94
		US-A-	5328922	12-07-94
WO-A-9404533	03-03-94	AU-B-	4704693	15-03-94
		CA-A-	2142721	03-03-94
		CN-A-	1086819	18-05-94
		SI-A-	9300438	31-03-94